Eur. J. Clin. Chem. Clin. Biochem.
Vol. 30, 1992, pp. 585–593

The Origin of Clinical Laboratories*)

By *J. Büttner*

Institut für Klinische Chemie I im Zentrum Laboratoriumsmedizin, Medizinische Hochschule Hannover, Germany

(Received May 14/July 10, 1992)

Summary: Clinical laboratories are a main attribute of clinical chemistry. Their historical development is therefore of great interest in the history of clinical chemistry. The results of a study are given which was undertaken to trace the establishment of clinical laboratories in central Europe, mainly in France, England and in the German-speaking countries. Presuppositions for the creation of these laboratories were:

(i) The idea that the results of laboratory examinations can be used as "chemical signs" in medical diagnosis, and

(ii) a new concept of disease which was the result of the "birth of the clinic" at the end of the 18th century.

The study shows that the development of clinical laboratories began 200 years ago. Up to the end of the 19th century, three development phases can be distinguished: an early phase from 1790 to 1840, a phase of institutionalization from 1840 to 1855, and a phase of extension between 1855 and 1890. To characterize these three phases, the foundation of the laboratories, the layout of the laboratory rooms, their equipment and instrumentation, and the usual staff are described with the aid of typical examples.

Introduction

In the middle of the last century *Claude Bernard* (1813–1878) referred to the laboratory as the "sanctuaire réel", the true sanctuary, of scientific medicine (1). This assessment found wide acceptance but also some criticism, because the sick person and not the laboratory should be the centre of the physician's work. The further development led to the laboratory becoming a characteristic feature of modern medicine. The medical historian *Erwin Ackerknecht* defines present-day medicine as "laboratory medicine", as distinct from "hospital medicine" of the preceding period (2).

The laboratory is certainly a specific attribute of clinical chemistry. It is therefore important to the self-conception of this discipline to investigate the historical development of the laboratory. A study was undertaken to trace the origin of clinical laboratories and their development in the early 19th century. The study was restricted to France, England and the German-speaking countries (3, 4).

The term "clinical laboratory" used in this study needs a more exact definition: it means a laboratory which is located in a hospital and serves directly for the care of the sick, primarily by assisting diagnosis. Laboratories may be fitted out for experiments of various types, for example physical, chemical, biological, etc. In the following we shall restrict ourselves to chemical laboratories.

Presuppositions for the Creation of Clinical Laboratories

Frequently, a historical development begins after fulfillment of certain presuppositions. Two main conditions are apparent for the creation of chemical laboratories in hospitals and clinics. Firstly, chemistry had

*) Based on a lecture given at the Symposium "History of Clinical Chemistry in Europe" of the IX European Congress of Clinical Chemistry, Cracow, Poland, September 1991.

to be able to assist the physician's diagnosis of diseases. This was certainly not the case for a long period in the history of chemistry. It was only at the end of the 18th century, in conjunction with the "revolution of chemistry" which is linked with the name of *Antoine Laurent Lavoisier* (1743–1794), that a change took place here. The organic compounds became better known and methods for the examination of these substances were developed. Above all, the quantitative determination of components of body materials became possible. Using these new techniques "chemical signs of disease" could be defined which were useful for the physician's diagnosis (for a more detailed discussion of the historical development of the concept of "chemical signs" see l. c. (5)).

The other condition which had to be fulfilled before clinical laboratories came into existence is substantially more complex and can be explained only in a brief excursion into the concept of "clinic". The word "clinic" means *teaching at the sick bed* (from the Greek κλίνη = bed). The term then also denotes the establishment in which this teaching takes place, e. g. a teaching hospital (6). At the end of the 18th century the concept "clinic" underwent a change important to the development of medicine. A new teaching concept for the study of medicine was developed which was based on observation and investigation. An important prerequisite for this concept was the creation of large hospitals in which a great number of sick people could be tended and treated. Such hospitals were built in France during the revolution, in the course of the reshaping of the health system. These new hospitals with their large number of patients were excellently suited for the new teaching concept. The diseases were presented to the students "in nature". They were able to make comparative studies of a larger number of patients suffering from the same disease. In addition, there was the regular performance of autopsies and pathological anatomical investigations which were easier to organize in the large hospitals. The new concept of the "clinic" led to a novel way of looking at disease. Disease was no longer considered to be the individual "illness" of a single patient but understood as an abstract concept, as it were an "entity of disease". The French philosopher *Michel Foucault* has named this epistemological change "the birth of the clinic" (7). Methods which were as objective as possible were sought for the exact and uniform description of a disease. The new natural scientific methods were particularly suited to this purpose. Thus, the "new clinic" had become ready to absorb the idea of applying physical and chemical investigation methods to medical diagnosis. There were differing opinions on the choice of suitable methods. For practical diagnosis, French clinicians preferred in particular physical methods, such as auscultation and percussion. In Germany, the Würzburg clinician *Johann Lucas Schoenlein* (1793–1864) used the "natural history method" for the description of diseases. The ambition was to study diseases as plants and animals are studied by descriptive botany and zoology ("natural history") (8, 9). *Schoenlein* preferred chemical and microscopical investigating to characterize diseases. The interest in the introduction of chemical methods grew following the incorporation of a "chemical sign" into the definition of a disease for the first time by *Richard Bright* (1789–1858) in 1827 (10). He described albuminuria as the cardinal symptom of the *morbus* named after him.

For a description of the historical development of clinical laboratories up to the end of the 19th century a distinction can be made between three phases, an early phase between 1790 and 1840, a phase of institutionalization between 1840 and 1855 and a phase of extension from 1855 onwards.

Early Phase of the Origins of Clinical Laboratories (ca. 1790–1840)

The idea of setting up laboratories in hospitals was expressed for the first time 200 years ago. The French physician and chemist *Antoine François Fourcroy* (1755–1809) (11) proposed in 1791 that in hospitals "a chemical laboratory should be set up not far away from a ward having twenty or thirty beds" (12, 13). In this laboratory, "excretions, urine and various discharges of the sick" should be subjected to a chemical analysis. He recommended that these examinations be made the job of young physicians, who were well trained in modern natural sciences. In such investigations, *Fourcroy* saw a new means of investigating the nature of diseases. His proposal was implemented in the following decades, at least in some of the Paris teaching hospitals. However, these laboratories were used almost exclusively for clinical research and teaching (see o. c. (14)).

What kinds of instruments and apparatus were used in a laboratory devised for the analysis of "animal material" at the end of the 18th century? A description of the typical apparatus used for chemical analysis is given by *Lavoisier* in his classical textbook "Traité élémentaire de chimie" (15). Of great importance were the new techniques for the analysis of gases developed by him. These include the analysis of gas mixtures and the first procedure for the elementary analysis of organic compounds. Indications of some more spec-

ialized instruments can be found in *Fourcroy*'s numerous experimental papers on animal chemistry (16). In his proposal for a clinical laboratory (12) *Fourcroy* also mentioned some instruments for physiological examinations, e. g. the balance invented by *Santorio Santorio* (1561–1636) (17) and instruments for the *in-vivo* analysis of respiratory gases (18). Table 1 summarizes the equipment of a laboratory according to *Fourcroy*'s proposal.

Tab. 1. Equipment of a laboratory provided for chemical and physiological examinations at the end of 18th century

Apparatus	Examples
Lamps	*Argand*'s oil lamp, spirit lamp
Furnaces	
Apparatus for handling and analysis of gases	"Appareils pneumato-chimique" (mercury bath (pneumatic trough), receivers, gasometer, *Woulfe* bottles) Eudiometer (oxygen determination)
Apparatus for preparative work	Filtration, decantation, lixiviation, evaporation, crystallization
Apparatus for distillation	Alembics, flasks, "cucurbits", retorts
Hydrometer (areometer)	"Pèse-liqueur"
Barometer	
Thermometer	
Balance	
Apparatus for physiological examinations	Balance according to *Santorio* Instruments for analysis of respiratory gases

In Germany as well people started to think about a reform in medicine. In 1803 in Halle, *Johann Christian Reil* (1759–1813) suggested in a plan for the "ideal medical college" that a clinical laboratory be set up (19). *Reil* had spent much time investigating the possibilities of "animal chemical investigations". He suggested that the hospital dispensary be given a small laboratory and the apothecary assigned the task of investigating "all pathological that can be chemically investigated, the different concrements in the body, the urine in diabetes, in dropsy, in stone diseases, in high fevers, the expectorations in pulmonary consumption, pneumonia, diphtheria, the sweat in miliary fever, rheumatism, intermittent fever, and actually all discharges and their relation to the kind of the disease, its character and course, and to the medicaments applied" (20).

In 1806 *Reil* then set up at the *Schola clinica* in Halle a "chemical physical investigation department" and succeeded in getting a chemist as its director (21). In 1810, when *Reil* was called to the newly founded university of Berlin a clinical laboratory was established there as well but due to the sudden death of *Reil* existed only for a short time (22).

In the plans of *Fourcroy* and *Reil* for the creation of clinical laboratories the main interest was devoted to research and teaching. For practical diagnostics at the sick bed, however, it was initially not necessary to use a separate working room for applying chemical methods. The simple chemical tests which were available in the first decades of the 19th century could be carried out at the sick bed with little apparatus. *Richard Bright* emphasized that to detect albuminuria all that was needed was a "candle and a teaspoon" (23). From 1817 onwards it was in London that particular attention was paid to the practical diagnostic application of chemical tests. *Alexander Marcet* (1770–1822) started with the qualitative chemical examination of concrements ("calculi") at the sick bed in order to diagnose "calculosis" (24). *William Prout* (1785–1850) developed a simple test programme for urine which he applied in his prescription room in Piccadilly for diagnosing diabetes and diseases of the urinary tracts (25). In the third decade of the 19th century it was in particular *Guy*'s Hospital in London, the house where *Richard Bright* and *Thomas Addison* (1793–1860) were active, which became a place where chemical diagnostics at the sick bed were practiced (26). However, it was not until 1842 that a separate small laboratory was set up there, as "research laboratory" for the kidney patients of the hospital (27).

Due to the limited analytical possibilities, the equipment of the laboratories or working places were still very simple. An excellent idea of them is provided by a drawing by *Alexander Marcet* which shows the apparatus for chemical diagnostic examinations of stones and urine (fig. 1) (28).

The early phase of the development of clinical laboratories in the period from about 1790 to 1840 can be summarized and characterized as follows: Chemical tests for diagnosis were only carried out occasionally in this phase. Separate laboratory rooms were hardly available. The investigations were performed at the bedside and were mainly of a qualitative nature. The equipment necessary for that purpose was very simple and consisted essentially of a few reagents and some glass apparatus. A few well equipped laboratories existed. They were used mainly for research and teaching. The examinations were carried out by the physicians themselves, although some were already being done by apothecaries or chemists (29).

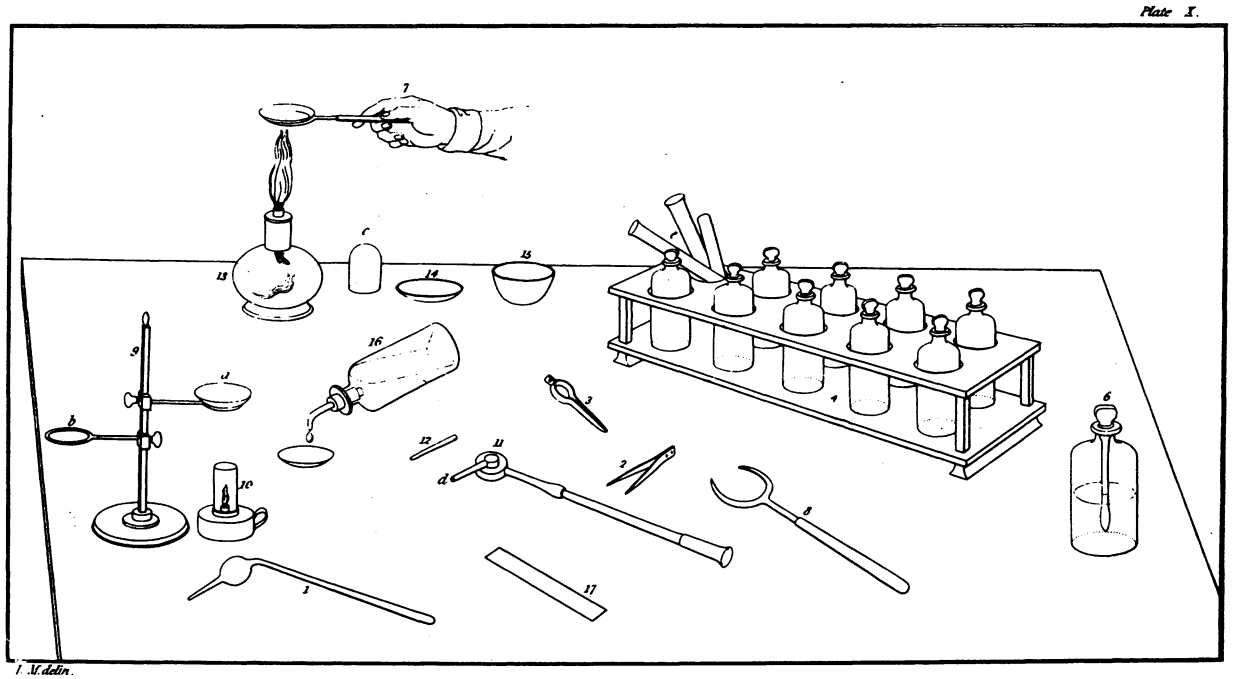

Fig. 1. "Apparatus adapted to the examination of all kinds of urinary calculi" (From *Marcet* (24), Plate X)
Explanation:

1. A common glass blow-pipe.
2 & 3. Small platina tongs.
4. A tray, containing test-bottles and tubes.
6. Test-bottle, with a glass tube attached to the stopper, for the purpose of taking out one drop of the solution.
7. Shows the mode of suspending watch-glasses, or cups, over the lamp, by means of an appropriate support.
8. The support used for the above purpose.
9. A stand to support watch-glasses, or cups, over a lamp.
10. An appropriate lamp.
11. Blow-pipe, made of brass.
12. A platina tip fitting the blow-pipe in d.
13. A spirit lamp, with a glass cup, c, to cover it, when not used.
14. & 15. Watch-glass, and glass capsule.
16. A bottle, with a tube through its cork, to obtain water drop by drop.
17. A slip of common window-glass.

Institutionalization Phase of Clinical Laboratories (ca. 1840–1855)

Around 1840, a second phase in the development of clinical laboratories started. At this time, chemical knowledge of organic compounds and their analysis had progressed to such an extent that the performance of chemical analyses for practical medical diagnostics was attracting greater interest. It was now that more involved quantitative methods began to be employed. These made larger laboratories necessary. Consequently in the German-speaking area in brief succession *independent* clinical laboratories were set up at various university hospitals, for example in Würzburg, Vienna and Berlin.

In the Würzburg Juliusspital (30) in 1841 a "chemical apparatus" for chemical examinations had been acquired, that is some instruments for chemical tests. In the following year this apparatus served as the basis for an independent clinical laboratory. To substantiate the need for such a laboratory, the clinicians drew attention to the great significance of "anthropochemistry", that is chemistry of the human organism, both for the diagnosis of diseases and for pathology, i.e. the understanding of diseases (31). The extraordinary professor for organic chemistry, *Johann Joseph Scherer* (1814–1869) was appointed as director of the Würzburg laboratory. His tasks expressly included "execution of the chemical examinations necessary for the clinics of the Juliusspital" (32). For this laboratory, which consisted initially of a small room, the term "clinical chemical laboratory" was coined for the first time. *Scherer* was a physician but had subsequently studied chemistry and concluded his education by spending one year as private assistant in the famous laboratory of *Justus Liebig* (1803–1873) in Giessen (33).

At the General Hospital in Vienna in 1844, a laboratory was established for pathological chemical examinations and was placed in the hands, provisionally at first, of the chemist *Johann Florian Heller* (1813–1871) (34). *Heller* did not win recognition with all clinicians. It was not until 1855 that he was given a permanent appointment. The laboratory was larger than that in Würzburg and consisted of three rooms (35, 36).

In 1839 *Johann Lucas Schoenlein* was called to the chair for clinical medicine at the Berlin University. At his instigation, the practice was started of performing chemical tests at the sick bed. They were performed by the apothecary and chemist *Johann Franz Simon* (1807–1843) (37). A suitable room for a laboratory was not available in the Charité hospital. This led *Simon* to set up a private laboratory in his nearby apartment, in which he performed tests for patients but also held private courses in chemical analysis for the physicians of the clinic. *Schoenlein* did not give his clinical teaching in the lecture hall but at the sick bed. It was *Simon*'s job to demonstrate chemical and microscopic examinations during *Schoenlein*'s clinical lectures. A separate clinical laboratory was first set up in 1859 by *Schoenlein*'s successor, *Friedrich Theodor Frerichs* (1819–1885); we shall return to that later.

The different types of apparatus in the laboratories of this period are known to us from books, papers published in journals, and from some documents in archives (38). Since the directors of the laboratories had mostly completed a special study in analytical chemistry, they sought to equip them with modern apparatus, including in particular instruments for performing quantitative analyses. Preparative work for isolating substances from biological material was however also possible. In table 2 a summary is given of the typical equipment. The investment costs for a well-equipped laboratory of this type were between about 700 and 1500 Prussian Reichsthaler (Rtl.) (39). As a comparison, the annual salary of an Ordinarius (full professor) at Prussian universities at that time was about 1500 to 2000 Reichsthaler.

Tab. 2. Typical equipment of a clinical chemical laboratory between ca. 1840 and 1855

Apparatus	Examples
Lamps	Spirit lamp, *Berzelius* lamp (1835)
Furnaces	*Sefström*'s "blast" furnace
Baths	
Water (baine Marie)	*Berzelius*' water bath *Liebig*'s water bath
Air	Copper air bath (*Liebig*, Giessen)
Sand	
Glass and porcelain ware	Tubes, flasks, funnels, beakers
Distillation apparatuses	
Apparatus for handling and quantitative analysis of gases	Air pump Pneumatic trough Gasometer (*Pepys*, 1802) Eudiometer (*Volta*, *Ure*, *Mitscherlich*)
Blow pipe	
Balances	Apothecaries' balance Fine balance (sensitivity < 1 mg)
Apparatus for organic analysis	*Liebig*'s combustion furnace with 5-bulb potash apparatus (1835), *Will*'s apparatus for nitrogen determination (1841)
Hydrometer (Areometer)	
Microscope	*Oberhäuser* (Paris), *Plössl* (Wien), *Schieck* (Berlin)
Polarimeter	*Biot-Soleil* (Paris, 1842, 1845), *Mitscherlich* (Berlin, 1844)

The phase of institutionalization in the development of clinical laboratories can be briefly characterized as follows: Clinical chemical laboratories were created as independent institutions, above all in university hospitals in the German-speaking area. This phase covered a period from 1840 to about 1855. The direction of these institutions was placed in the hands of natural scientists (40). The laboratories were still very restricted in space but their equipment made it possible to perform in professional manner pathological chemical analyses corresponding to the "state of the art". Apart from performing analyses for the hospital, an important task of these laboratories was the practical training of physicians and medical students in physiological and pathological chemistry.

Phase of the Extension of Clinical Laboratories (from About 1855 Onwards)

From about 1855 onwards, a third phase begins in the development of clinical laboratories in which a spreading out of such laboratories occurs. There are various reasons which can be given for this. At that time, first successes of the new medicine based on the natural sciences were becoming apparent. In Germany, under the concept of "pathological physiology" medical research based entirely on experiment was developing. A group of young physiologists under the guidance of *Hermann Helmholtz* (1821–1894) and *Carl Ludwig* (1816–1895) were attempting to explain physiological phenomena completely on the basis of natural physical and chemical laws. In France, in particular through *Claude Bernard*, a very successful experimental physiology had been developed. We have already cited at the beginning his saying that the laboratory is the true sanctuary of scientific medicine. A great influence was also exerted by the books of *Justus Liebig*; in particular, they stimulated the use of chemical methods in medical research (41).

These changes led to an awakening interest of the clinicians in chemical work (42). As a result, in the latter decades of the 19th century an increasing number of chemical laboratories for medical purposes came into being. In retrospect, the clinician *Bernard Naunyn* (1839–1925) said: *"Setting up a laboratory for his clinic soon became a point of honour to the clinician"* (43). However, characteristic national differences can be observed. It is in particular striking that alongside the chemical laboratory in the clinic, as described for the previous phase (for example in Würzburg, Vienna or Berlin), other forms of medical laboratory came into existence.

In the German-speaking area the clinical laboratory in the hospital became a general standard. In the new buildings for university clinics which were erected in many places from 1880 onwards (44), the laboratory was very frequently given a central location. A typical example of this is the laboratory of the Medical Clinic in Giessen (45) which was inaugurated in 1890 (fig. 2). Here, a large laboratory is found on the ground floor opposite the entrance staircase: The laboratory as a temple of scientific medicine. The laboratory area is about 150 m^2, of which 23 m^2 is allocated to the clinic director as a private research laboratory. These laboratories were used only to a small extent for diagnostic routines. They were intended in particular *"for scientific work in the field of clinical medicine"* (46), i.e. for experimental work in the research of diseases. In this connection, *Naunyn* remarked: *"The hospital ward is the most fruitful source of subjects for normal and pathological physiology"* (47). The hospital laboratories of university clinics were under the charge of the clinic director. In Berlin in 1859, *Frerichs* appointed a *"chemical laboratory assistant"* (48, 49) in the Clinic. From about 1890 onwards, in the university clinics, in addition to the clinic laboratory, so-called ward laboratories were increasingly set up for the routine analyses necessary for diagnosis. They served primarily for the training of young physicians of the clinic (interns) and of the "Amanuenses" (Famuli) who themselves had to perform the necessary laboratory tests for the patients entrusted to them (50, 51).

In France, the tasks of the hospital laboratory were performed mainly by the usually quite well equipped laboratories of the hospital apothecaries. As already explained, such a proposal had been made 50 years earlier by *Reil*. More exact historical investigations are needed to determine why only a few clinical laboratories run by physicians were set up in France. Possibly, since French clinicians were less interested in chemical than in physical or physiological methods, they did not perform chemical tests themselves, but, in contrast to German clinicians, left them to the apothecary.

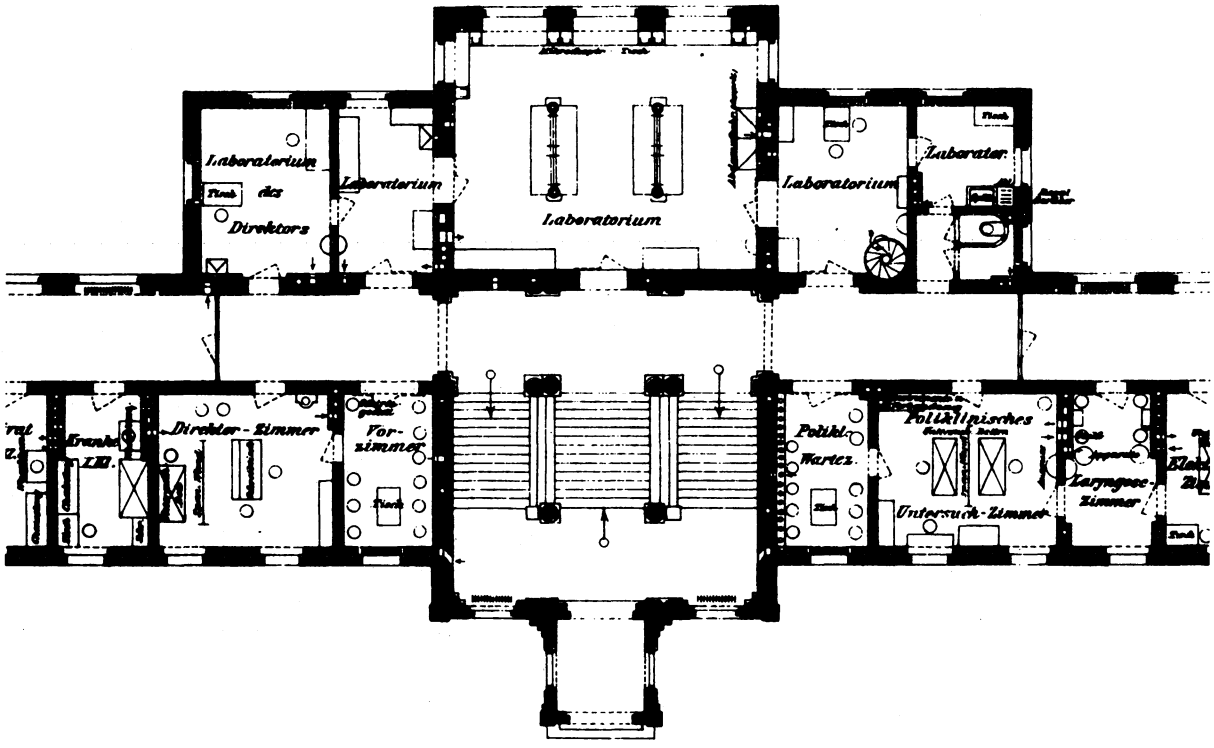

Fig. 2. Clinical Laboratory of the Medical Clinic of the Giessen University (1890). Detail of the centre of the ground floor: The Clinical Laboratory in the upper part of the picture (From l.c. (45)).

We still have to mention a special type of laboratory which originated at the Berlin University and was subsequently copied in particular in the USA (52). *Rudolf Virchow* (1821–1902), following his call to the chair for pathological anatomy in 1856, set up a "chemical department" within the Institute for Pathology and put *Felix Hoppe(-Seyler)* (1825–1895) in charge of it. This laboratory was very well equipped and up to the twenties of the twentieth century represented a centre of clinical chemical research.

The apparatus of laboratories in this third phase was not as extensive as in the preceding period (tab. 3) (53). This is due in part to the fact that the typical equipment of a general chemical laboratory is lacking. For example, hardly any furnaces, distillation apparatuses, etc., are found. Instead, the standard equipment soon included some important physical measuring devices such as spectroscopes, colorimeters, spectrophotometers, etc. In addition, there was apparatus required for specific research tasks, for example a *Pflüger* gas pump for investigating blood gases (54). The figures found for the costs involved in fitting out a smaller laboratory without special apparatus are 300 Rtl. (55) or 400 Gulden (fl) (56), i.e. substantially less than in the preceding period. From about 1880 onwards, apparatus for bacteriological investigations was increasingly included, but it will not be discussed here.

The extension phase of clinical laboratories is characterized as follows. Clinical laboratories spread rapidly. The organization of the laboratories was very different from country to country. A typical development in German-speaking countries was the hospital laboratory, serving in university hospitals primarily for clinical research and teaching. For clinical routine and for training students, so-called ward laboratories were set up. In contrast to the preceding phase, the clinical laboratories were under the directorship of clinicians.

Tab. 3. Equipment of a larger clinical laboratory between ca. 1855 and 1890

Apparatus	Examples
Lamps	Spirit lamp *Bunsen*'s gas burner (1857)
Baths for applying heat	
Water bath	Water bath according to *Liebig*
Air	Copper air bath (*Liebig*)
Sand	
Glassware	Test tubes, flasks, funnels, beakers Measuring flasks
Instruments for volumetric analysis	*Gay-Lussac*'s burette (1824) *Mohr*'s burette with pinchcock (1853) Pipettes
Balance	Fine balance (sensitivity < 1 mg)
Centrifuge	Haematocrit (*Hedin*, 1890) Centrifuge for urinary sediment (*Stenbeck*, 1892)
Spectroscope	"Small spectral apparatus for chemists" according to *Kirchhoff* and *Bunsen* (1862) Pocket spectroscope (*Browning*, London, 1870)
Colorimeter	*Duboscq*'s colorimeter (1854) *Fleischl*'s haemometer (1885)
Photometer for quantitative spectral analysis	*Vierordt* (1873) *Hüfner* (1877)
Microscope	*Oberhäuser* (Paris), *Plössl* (Wien), *Schieck* (Berlin)
Polarimeter	*Biot-Soleil* (Paris, 1842, 1845), *Mitscherlich* (Berlin, 1844)

Tab. 4. The origin of clinical laboratories (Summary)

I. Early Phase	ca. 1790–1840
First concepts of clinical laboratories (*Fourcroy* 1791, *Reil* 1803)	
Simple bedside testing methods for the examination of stones, urine, (blood)	
II. Phase of institutionalization	ca. 1840–1855
Examples: Würzburg (1842), Vienna (1844), Berlin (1839)	
Qualitative and quantitative chemical analysis of urine, blood and other materials	
Physiological and pathological chemical research and training	
III. Phase of extension	ca. 1855–1890
Hospital laboratories, ward laboratories, laboratories of hospital pharmacies, chemical departments of pathological institutes	
Development of specialized clinical chemical methods Pathophysiological and clinical research Routine examinations for diagnostic purposes	

Conclusion

In table 4, the three development phases of clinical laboratories outlined are briefly summarized. Within the course of 100 years, the development which started 200 years ago with a proposal by *Fourcroy* had led to institutions with modern equipment, although cramped in space. It is important to notice that from the start clinical laboratories were used not only to assist in caring for the sick but at the same time to perform important functions in research and teaching. This should be an inspiration and obligation to us today.

Remarks and References

1. Bernard, C. (1865) *Introduction à l'étude de la médecine expérimentale*. J. B. Baillière & Fils, Paris, p. 394.
2. Ackerknecht, E. H. (1950) Elisha Bartlett and the philosophy of the Paris clinical school. Bull. Hist. Med. *24*, 45–60.
3. Büttner, J. (1989) Die Entstehung klinischer Laboratorien in den deutschsprachigen Ländern im 19. Jahrhundert. In: *Johann Christian Reil (1759–1813) und seine Zeit* (Kaiser, W. & Völker, A., eds.) Martin-Luther-Universität Halle Wittenberg, Wiss. Beitr. 1989/T 73, Martin-Luther Universität Halle-Wittenberg, Halle (Saale), pp. 118–135.
4. Büttner, J. (1990) "Le santuaire réel". Die Entstehung Klinischer Laboratorien im 19. Jahrhundert. Deutsche Ges. f. Klin. Chemie – Mitteilungen *21*, 53–60.
5. Büttner, J. (1991) Leitgedanken in der Geschichte der Klinischen Chemie. Medizinhist. J. *25*, 268–285.
6. Meyer's Conversations-Lexikon, Original Ausgabe (1851) Bibliographisches Institut, Hildburghausen, Band *18*, p. 110.
7. Foucault, M. (1972) *Naissance de la clinique*. 2me édition. – Paris: Presse Universitaire de France.
8. About Schoenlein and his "natural history method" see: Bleker, J. (1981) *Die Naturhistorische Schule 1825–1845. Ein Beitrag zur Geschichte der klinischen Medizin in Deutschland* (Medizin in Geschichte und Kultur, vol. 13). G. Fischer Verlag, Stuttgart–New York.
9. Büttner, J. (1989) Historische Voraussetzungen für die Entstehung der Klinischen Chemie. Wien. Klin. Wochenschr. *101*, 101–104.
10. Bright, R. (1827–1831) *Reports on Medical Cases Selected with a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy*. Vol. 1. Longman, London, pp. 1 ff.
11. About Fourcroy and his importance for Clinical Chemistry see:
    (a) Büttner, J. & Habrich, C. (1887) *Roots of Clinical Chemistry*. GIT-Verlag, Darmstadt;
    (b) Habrich, C. (1985) Antoine François de Fourcroy (1755–1809) Studien zu einem neuentdeckten Portrait. In: *Orbis Pictus. Kultur- und pharmaziehistorische Studien* (Dressendörfer, W. & Müller-Jahncke, W.-D., eds.) Govi-Verlag, Frankfurt am Main, pp. 145–163.
12. Fourcroy, A. F. (1791) Idées sur un nouveau moyen de rechercher la nature des maladies. La Médecin éclairée par les sciences physique [Paris] *1*, 142–145.
13. Büttner, J. The programme devised in 1791 by Fourcroy for the establishment of clinical laboratories. Tractrix [Utrecht], in press.
14. Lesch, J. E. (1984) *Science and Medicine in France. The Emergence of Experimental Physiology, 1790–1855*. Harvard University Press, Cambridge (Mass.), London.
15. Lavoisier, A. L. (1789) *Traité élémentaire de chimie, présente dans un ordre nouveau et d'après les découvertes modernes*. 2 volumes. Cuchet, Paris.
16. Fourcroy analyzed a large number of animal materials, partly together with Nicolas Vauquelin (1763–1829). For a review and complete bibliography see: Smeaton, W. A. (1962) *Fourcroy. Chemist and revolutionary 1755–1809*. Cambridge, W. Heffer & Sons, pp. 136 ff.
17. Santorio Santorio used the balance for investigating the *perspiratio insensibilis*. See: Santorio Santorio (1614) *Ars [...] de statica medicina*. Apud N. Polum, Venetiis.
18. Fourcroy proposed to measure the quantity of carbonic acid and nitrogen of the expired air and the change of oxygen content of the inspired air. This refers to the famous experiments made by Lavoisier and Seguin in 1789. See: Seguin, A. & Lavoisier, A. L. (1789) Premier mémoire sur la respiration des animaux. Mémoires du Académie de Sciences [Paris] *1793*, 566–584 (read 1789).
19. Beneke, R. (1913) *Johann Christian Reil. Gedächtnisrede bei der von der Friedrichs-Universität veranstalteten Erinnerungsfeier für den vor 100 Jahren Dahingeschiedenen*. Max Niemeyer, Halle, pp. 48–55.
20. L. c. (19), quotation p. 55 (translated from German).
21. The first director of the "Chemisch-physikalische Untersuchungsanstalt" was Adolf Ferdinand Gehlen (1775–1815). See: Habrich, C. (1989) Zur Typologie des Chemiker-Apothekers im frühen 19. Jahrhundert: Adolph Ferdinand Gehlen (1775–1815). In: *Johann Christian Reil (1759–1813) und seine Zeit* (Kaiser, W. & Völker, A., eds.) Martin-Luther-Universität Halle Wittenberg, Wiss. Beitr. 1989/T 73, Martin-Luther Universität Halle-Wittenberg, Halle (Saale), pp. 211–217.
22. As director of this laboratory, Reil appointed Georg Karl Ludwig Sigwart (1784–1864) who had habilitated under him in Halle (1810). See:
    (a) Simmer, H. (1955) Aus den Anfängen der physiologischen Chemie in Deutschland. G. K. L. Sigwart (1784–1864) und J. E. Schloßberger (1819–1860). Sudhoffs Archiv, Z. f. Wissenschaftsgeschichte *39*, 216–236;
    (b) Sepke, H. & Sepke, I. (1985) Zu den Anfängen der physiologischen Chemie an der Berliner Universität. Die Bedeutung J. Ch. Reils und G. K. L. Sigwarts für die Entwicklung der klinischen Chemie. Z. Gesamte Hyg. Ihre Grenzgeb. *31*, 651–642;
    (c) Müller, Th. (1991) *Über die Anfänge der klinischen Chemie an der Berliner Universität (1810–1813) – Georg Carl Ludwig Sigwart (1784–1864) als Pionier einer neuen Wissenschaftsdisziplin*. Medical Thesis, Humboldt-Universität Berlin.
23. O. c. (10), vol. 1, p. 3.
24. Marcet, A. (1819) *An Assay on the Chemical History and Medical Treatment of Calculous Disorders*. 2nd Edition (1st Edition 1817). Longman, Hurst, Orme, Brown, London.
25. Prout, W. (1821) *An Inquiry into the Nature and Treatment of Gravel, Calculus and other Diseases of the Urinary Organs*. 1st Edition. Baldwin, Cradock and Joy, London.
26. Particularly George Owen Rees (1813–1889) and Golding Bird (1814–1854), physicians at Guy's Hospital were engaged in this work. See:
    (a) Coley, N. G. (1986) George Owen Rees, MD, FRS (1813–89): Pioneer of medical chemistry. Med. Hist. *30*, 173–190;
    (b) Coley, N. G. (1969) The collateral sciences in the work of Golding Bird. Med. Hist. *13*, 363–376.
27. About 1842, two wards having 18 and 24 beds were reserved specifically for patients suffering from kidney diseases. A room located between the wards was equipped as a small laboratory, "fitted up and decorated entirely to our purposes [...] Dr. Rees had charge of the laboratory, in which he was assisted by Mr. Pearce". (Bright in the foreword to a paper by Barlow and Rees). See:
    Barlow, G. H. & Rees, G. O. (1843) Account of observations made under the superintendence of Dr. Bright, on patients whose urine was albuminous. Guy's Hosp. Rep. [2nd Series] *1*, 189–316. quotation pp. 189–190. See also: Bright, Pamela (1983) *Dr. Richard Bright (1789–1858)*. The Bodley Head, London, Sydney, Toronto, p. 220.
28. O. c. (24), Plate X.
29. For the professional background of people engaged in clinical laboratories see:
    (a) Hickel, E. (1983) The emergence of Clinical Chemistry in 19th century: Presuppositions and consequences. In: *History of Clinical Chemistry* (Büttner, J., ed.) Walter de Gruyter, Berlin–New York, pp. 35–43;
    (b) Büttner, J. (1985) Wechselbeziehungen zwischen Chemie und Medizin im 19. Jahrhundert. In: *Jahrbuch des Instituts für Geschichte der Medizin der Robert-Bosch-Stiftung* (Wittern, R., ed.) vol. 2 (1983). Hippokrates Verlag, Stuttgart, pp. 7–24.

30. For the history of the Würzburg Institute see:
(a) Büttner, J. (1978) Johann Joseph von Scherer (1814–1869). Ein Beitrag zur frühen Geschichte der Klinischen Chemie. J. Clin. Chem. Clin. Biochem. *16*, 478–483.
English translation in: Büttner, J. [Editor] (1983) *History of Clinical Chemistry.* W. de Gruyter, Berlin/N. Y., pp. 45–50;
(b) L. c. (3).
31. Report of Hofrath and Prof. Dr. v. Marcus to the Academic Senate of Würzburg University of 9. 3. 1842. Akten des Rektorats und Senats Nr. 795, University Library Würzburg.
32. Decree relating to Scherer's appointment, signed by Ludwig I on 17. 7. 1842. Akten des Rektorats und Senats Nr. 795, University Library Würzburg.
33. For the biography of Scherer see o. c. (11a) and l. c. (30a).
34. For the biography of Heller see o. c. (11a).
35. Schmalhofer, J. (1980) *Das Werk von Johann Florian Heller mit besonderer Berücksichtigung der Entstehung des ersten pathologisch-chemischen Laboratoriums am Allgemeinen Wiener Krankenhaus und der Ernennung Hellers.* Medical Thesis, University of Bonn.
36. Prosper Ménière, who visited the laboratory, spoke of an "institution not having its like in France": Ménière, (P.) (1851) Une promenade en Allemagne. À M. le docteur Jules Guérin. Gazette médicale de Paris 1851, 731–738.
37. For the development of Schönlein's Clinic and on Simon see l. c. (3) and o. c. (11a).
38. For details see: l. c. (3) and o. c. (11a).
39. Heintz, W. (1847) Plan for the equipment of a pathological chemical laboratory at the Charité in Berlin from 16. 5. 1847 (the laboratory was planned on the first floor of the "Leichenhaus" (morgue). Heintz prepared detailed plans for this laboratory). Zentrales Staatsarchiv Merseburg, Geheime Medicinal-Registratur, Rep. 76 VIII D Nr. 78 Vol. 2 fol. 105–156.
40. At that time the profession of the chemist was not clearly defined. In many cases people had a training as apothecary or finished a study of medicine before they entered a study of chemistry. See:
Hickel, E. (1978) Der Apothekerberuf als Keimzelle naturwissenschaftlicher Berufe in Deutschland. Medizinhist. J. *13*, 259–276.
41. (a) Liebig, J. (1840) *Die organische Chemie in ihrer Anwendung auf Agricultur und Physiologie.* Vieweg & Sohn, Braunschweig;
(b) Liebig, J. (1842) *Die organische Chemie in ihrer Anwendung auf Physiologie und Pathologie.* Vieweg & Sohn, Braunschweig.
42. For the development of chemical work in German Clinics see:
Büttner, J. (1982) Interrelationships between clinical medicine and clinical chemistry, illustrated by the example of the German-speaking countries in the late 19th. century. J. Clin. Chem. Clin. Biochem. *20*, 465–471.
32. Naunyn, B. (1925) *Erinnerungen, Gedanken und Meinungen.* J. F. Bergmann, München, p. 225.
44. Examples are: Gießen, Königsberg, Breslau, Straßburg, Leipzig, Bern, München, Heidelberg.
45. Riegel, F. (1894) Die klinischen Neubauten in Gießen. Klinisches Jahrbuch *5*, 126–137 (table 2).
46. Quotation from the User Regulations for the Medical Clinical Institute (Medizinisch-klinisches Institut) set up in Munich in 1878 by Hugo v. Ziemssen (1829–1902). See: Ziemssen, (H.) v. (1878) *Ueber die Aufgaben des Klinischen Unterrichts und der Klinischen Institute. Rede.* F. C. W. Vogel, Leipzig, p. 24.
47. O. c. (43), p. 235.
48. Letter from F. Th. Frerichs to the Minister v. Bethmann-Hollweg of 28. 4. 1859 Zentrales Staatsarchiv Merseburg, Geheime Medicinal-Registratur, Rep. 76 Va Sekt. 2 Tit. X No. 37 Vol. 2 fol. 73–74.
49. A permanent post was created for this purpose in 1868. It was initially the only civil physician post at the Clinic. All the other assistants at the Charité were military physicians. See: Zentrales Staatsarchiv Merseburg, Geheime Medicinal-Registratur, Rep. 76 Va Sekt. 2 Tit. IV No. 50 Vol. III fol. 34–36.
50. A detailed and illustrative description of clinical laboratories and ward laboratories in Germany is given by Abraham Flexner in his report:
Flexner, A. (1912) *Medical Education in Europe. A Report to the Carnegie Foundation for the Advancement of Teaching.* N. Y., Bulletin of the Carnegie Foundation 6, see for example p. 161.
51. Bleker, J. (1987–1988) Medical students – to the bedside or to the laboratory? The emergence of laboratory-training in German medical education 1870–1900. Clio Med. *21*, 35–46.
52. For the early history see l. c. (3).
53. L. c. (3).
54. Pflüger, E. (1865) Beschreibung meiner Gaspumpe. In: *Untersuchungen aus dem physiologischen Laboratorium zu Bonn.* A. Hirschwald, Berlin, pp. 183–188.
55. L. c. (48, 49).
56. For setting up a laboratory for the Würzburg clinician Heinrich Bamberger, 400 fl were granted as well as 50 fl/year for the running costs. See: Bericht der medicinischen Fakultät an den Senat vom 31. 1. 1859. Akten des Rektorats und Senats Nr. 356, University Library Würzburg.

Prof. Dr. Dr. J. Büttner
Institut für Klinische Chemie I
Medizinische Hochschule Hannover
Konstanty-Gutschow-Straße 8
W-3000 Hannover 61
Bundesrepublik Deutschland